1. Reversal of liver fibrosis by the antagonism of endocannabinoid CB1 receptor in a rat model of CCl4-induced advanced cirrhosis

By Giannone, Ferdinando A.; Baldassarre, Maurizio; Domenicali, Marco; Zaccherini, Giacomo; Trevisani, Franco; Bernardi, Mauro; Caraceni, Paolo
From Laboratory Investigation (2012), 92(3), 384-395. Language: English, Database: CAPLUS, DOI:10.1038/labinvest.2011.191

The endocannabinoid system is involved in the pathogenesis of liver fibrosis. Although many substances have been proved to reduce fibrosis in exptl. models of chronic liver injury, most of them appear to be effective only if given as a prophylactic or early treatment. This study aimed to explore the effect of pharmacol. antagonism of the endocannabinoid cannabinoid type 1 (CB1) receptor started after the stage of full-blown cirrhosis had been reached. Wistar-Han rats with carbon tetrachloride (CCl4)-induced cirrhosis were randomized to receive the CB1 receptor antagonist Rimonabant (10 mg/kg/day) or the vehicle for 2 wk. Age-matched healthy rats served as controls. Liver fibrosis was assessed using Sirius red staining, hydroxyproline concn. and α-smooth muscle actin expression. Hepatic gene expression of mediators of fibrogenesis and inflammation were evaluated by real-time PCR. We also assessed the hepatic expression of CB1 and CB2 receptors and that of the enzymes implicated in the endocannabinoid metab. Fibrosis was significantly reduced in rats treated with Rimonabant compared with rats receiving the vehicle. CB1 receptor antagonism limited the gene upregulation of fibrogenic and inflammatory mediators occurring in untreated cirrhotic rats. CB1 and CB2 receptor expression was increased in cirrhotic animals. Interestingly, pharmacol. CB1 receptor antagonism was assocd. with a further induction of the CB2 receptor expression. Regression of fibrosis can be achieved by pharmacol. blockade of the CB1 receptor even when started in an advanced stage of the disease. This effect is assocd. with the suppression of pro-fibrogenic and inflammatory mediators and may have been indirectly favored by the induction of CB2 receptor expression. Lab. Investigation (2012) 92, 384-395; doi:10.1038/labinvest.2011.191; published online 19 Dec. 2011.

~0 Citings

2. Cannabinoid receptor type I modulates alcohol-induced liver fibrosis

By Patsenker, Eleonora; Stoll, Matthias; Millonig, Gunda; Agaimy, Abbas; Wissniowski, Till; Schneider, Vreni; Mueller, Sebastian; Brenneisen, Rudolf; Seitz, Helmut K.; Ocker, Matthias; et al
From Molecular Medicine (Manhasset, NY, United States) (2011), 17(11-12), 1285-1294. Language: English, Database: CAPLUS, DOI:10.2119/molmed.2011.00149

The cannabinoid system (CS) is implicated in the regulation of hepatic fibrosis, steatosis and inflammation, with cannabinoid receptors: 1 and 2 (CB1 and CB2) being involved in regulation of pro- and antifibrogenic effects. Daily cannabis smoking is an independent risk factor for the progression of fibrosis in chronic hepatitis C and a mediator of exptl. alc. steatosis. However, the role and function of CS in alc. liver fibrosis (ALF) is unknown so far. Thus, human liver samples from patients with alc. liver disease (ALD) were collected for anal. of CB1 expression. In vitro, hepatic stellate cells (HSC) underwent treatment with acetaldehyde. H2O2, endo- and exocannabinoids (2-arachidonoylglycerol (2-AG) and Δ9-tetrahydrocannabinol [THC]), and CB1 antagonist SR141716 (rimonabant). In vivo, CB1 knockout (KO) mice received thioacetamide (TAA)/ethanol (EtOH) to induce fibrosis. As a result, in human ALD, CB1 expression was restricted to areas with advanced fibrosis only. In vitro, acetaldehyde, H2O2, as well as 2-AG and THC, alone or in combination with acetaldehyde, induced CB1 mRNA expression, whereas CB1 blockage with SR141716 dose-dependently inhibited HSC proliferation and downregulated mRNA expression of fibrosis-mediated genes PCα1(I), TIMP-1 and MMP-13. This was paralleled by marked cytotoxicity of SR141716 at high doses (5-10 μmol/L). In vivo, CB1 knockout mice showed marked resistance to alc. liver fibrosis. In conclusion, CB1 expression is upregulated in human ALF, which is at least in part triggered by acetaldehyde (AA) and oxidative stress. Inhibition of CB1 by SR141716, or via genetic knock-out protects against alc.-induced fibrosis in vitro and in vivo.

~0 Citings

3. Combination therapy for metabolic diseases using GLP-1 receptor agonists and a DPP-4 inhibitors

By Klein, Thomas; Grempler, Rolf; Mark, Michael
From PCT Int. Appl. (2011), WO 2011138421 A1 20111110, Language: English, Database: CAPLUS

The invention relates to methods for treating and/or preventing metabolic diseases, esp. type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analog such as exenatide) and a certain DPP-4 inhibitor (e.g. linagliptin).

~1 Citing

4. The endocannabinoid system as a key mediator during liver diseases: new insights and therapeutic openings

By Mallat, A.; Teixeira-Clerc, F.; Deveaux, V.; Manin, S.; Lotersztajn, S.
From British Journal of Pharmacology (2011), 163(7), 1432-1440. Language: English, Database: CAPLUS, DOI:10.1111/j.1476-5381.2011.01397.x

A review. Chronic liver diseases represent a major health problem due to cirrhosis and its complications. During the last decade, endocannabinoids and their receptors have emerged as major regulators of several pathophysiol. aspects assocd. with chronic liver disease progression. Hence, hepatic cannabinoid receptor 2 (CB2) receptors display beneficial effects on alc. fatty liver, hepatic inflammation, liver injury, regeneration and fibrosis. Cannabinoid receptor 1 (CB1) receptors were implicated in the pathogenesis of several lesions such as alc. and metabolic steatosis, liver fibrogenesis, or circulatory failure assocd. with cirrhosis. Although the development of CB1 antagonists has recently been suspended due to the high incidence of central side effects, preliminary preclin. data obtained with peripherally restricted CB1 antagonists give real hopes in the development of active CB1 mols. devoid of central adverse effects. CB2-selective mols. may also offer novel perspectives for the treatment of liver diseases, and their clin. development is clearly awaited. Whether combined treatment with a peripherally restricted CB1 antagonist and a CB2 agonist might result in an increased therapeutic potential will warrant further investigation.

~1 Citing

5. Cannabinoid receptor type 1 (CB1) antagonists for treating hepatitis C virus infection

By Van der Poorten, David; Douglas, Mark; George, Jacob
From PCT Int. Appl. (2011), WO 2011072336 A1 20110623, Language: English, Database: CAPLUS

The invention relates to agents for the treatment of hepatitis C virus infection. More specifically, the invention relates to antagonists of cannabinoid type 1 receptor signaling pathway proteins and their use for the treatment of hepatitis C virus infection. CB1 antagonists of the invention e.g. (S)-SLV-319, NIDA-41020 are administered along with one or more addnl. anti-HCV agents such as HCV protease inhibitor, an HCV polymerase inhibitor, an HCV caspase inhibitor.

~0 Citings

6. Endocannabinoids in the pathophysiology of obesity - the liver

By Mallat, Ariane; Lotersztajn, Sophie
From Drug Discovery Today: Disease Mechanisms (2011), 7(3-4), e185-e190. Language: English, Database: CAPLUS, DOI:10.1016/j.ddmec.2010.11.001

A review. With the increasing prevalence of obesity and comorbidities, non-alc. fatty liver disease (NAFLD) has become the most common cause of liver disease in Western countries. Clin. and exptl. studies have identified CB1 and CB2 receptors as potential novel therapeutic targets in the management of NAFLD. CB2 receptors in the adipose tissue probably participate in the pathogenesis of obesity-assocd. insulin resistance and nonalcoholic fatty liver disease. However, hepatic CB2 receptors display beneficial effects in various aspects of liver disease, including liver injury, regeneration and fibrosis. Hence, addnl. preclin. studies are warranted to define the contribution of adipose tissue vs. liver CB2 receptors during chronic liver diseases. Although the development of CB1 antagonists has recently been suspended due to an alarming rate of mood disorders, preliminary preclin. data obtained with peripheral CB1 antagonists give real hopes in the development of active CB1 mols. devoid of central adverse effects.

~0 Citings

7. Endocannabinoids in liver disease

By Tam, Joseph; Liu, Jie; Mukhopadhyay, Bani; Cinar, Resat; Godlewski, Grzegorz; Kunos, George
From Hepatology (Hoboken, NJ, United States) (2011), 53(1), 346-355. Language: English, Database: CAPLUS, DOI:10.1002/hep.24077

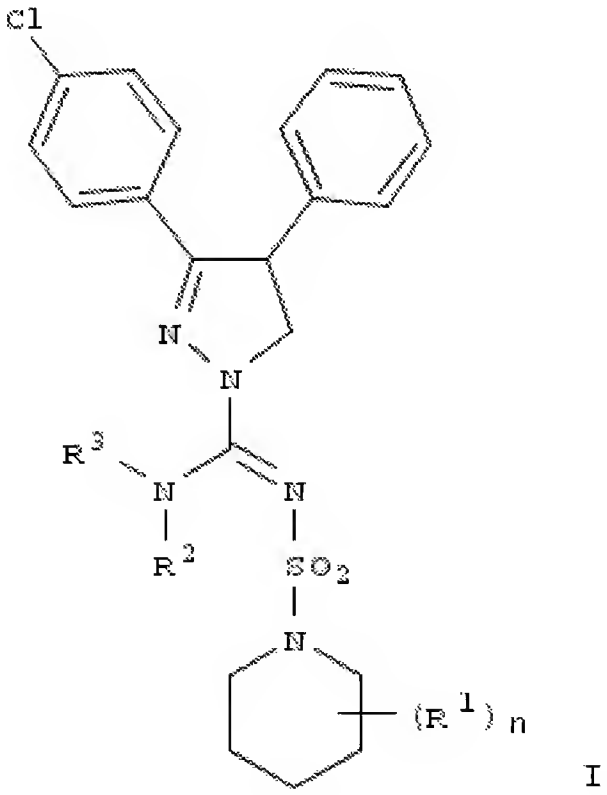
A review. Endocannabinoids are lipid mediators of the same cannabinoid (CB) receptors that mediate the effects of marijuana. The endocannabinoid system (ECS) consists of CB receptors, endocannabinoids, and the enzymes involved in their biosynthesis and degrdn., and it is present in both brain and peripheral tissues, including the liver. The hepatic ECS is activated in various liver diseases and contributes to the underlying pathologies. In patients with cirrhosis of various etiologies, the activation of vascular and cardiac CB1 receptors by macrophage-derived and platelet-derived endocannabinoids contributes to the vasodilated state and cardiomyopathy, which can be reversed by CB1 blockade. In mouse models of liver fibrosis, the activation of CB1 receptors on hepatic stellate cells is fibrogenic, and CB1 blockade slows the progression of fibrosis. Fatty liver induced by a high-fat diet or chronic alc. feeding depends on the activation of peripheral receptors, including hepatic CB1 receptors, which also contribute to insulin resistance and dyslipidemias. Although the documented therapeutic potential of CB1 blockade is limited by neuropsychiatric side effects, these may be mitigated by using novel, peripherally restricted CB1 antagonists.

~6 Citings

8. Preparation of fluoro-substituted 3,4-diaryl-4,5-dihydro-1H-pyrazole-1-carboxamidines having cannabinoid CB1 antagonist activity

By Lange, Josephus H. M.; Vliet, Van Bernard J.
From PCT Int. Appl. (2010), WO 2010003760 A2 20100114, Language: English, Database: CAPLUS

Title compds. (I; n = 1, 2; R1 = F, CF3; R2 = H, alkyl; R3 = H, Me), were prepd. Thus, N-[(4,4-difluoropiperidin-1-yl)sulfonyl]carbamic acid tert-Bu ester (prepn. given) was refluxed 3 h with 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole in PhMe to give 76% 3-(4-chlorophenyl)-N-[(4,4-difluoropiperidin-1-yl)sulfonyl]-4-phenyl-4,5-dihydropyrazolecarboxamide. This was refluxed 4 h with POCl3 and dimethylaminopyridine in CH2Cl2 followed by cooling, addn. of MeNH2.HCl and diisopropylethylamine, and stirring overnight to give 91% N-[(4,4-difluoropiperidin-1-yl)sulfonyl]-N'-methyl-3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. The latter showed CB1 receptor binding with Ki = 10 nM.



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~1 Citing

9. Cannabinoid receptor CB1 antagonists: state of the art and challenges

By Bifulco, Maurizio; Santoro, Antonietta; Laezza, Chiara; Malfitano, Anna Maria
From Vitamins and Hormones (San Diego, CA, United States) (2009), 81(Anandamide an Endogenous Cannabinoid), 159-189. Language: English, Database: CAPLUS, DOI:10.1016/S0083-6729(09)81007-8

A review. The discovery of cannabinoid receptors led to the development of several compds. targeted against these receptors. In particular, CB1 receptor antagonists have been described to possess key functions in the treatment of obesity and obesity-related pathologies. Numerous clin. trials revealed the advantage of strategies designed to block CB1 receptor but also evidenced the limitations due to side effects exerted by these substances. Recent studies have highlighted that CB1 antagonists could have other effects and find applications even in other pathologies like hepatic fibrosis, chronic inflammatory conditions, diabetes, and cancer. Since the suspending sales of the lead compd., rimonabant, and the discontinuation of all ongoing clin. trials of CB1 blockers, alternative strategies could emerge and lead to the development of further basic research studies to redirect these compds.

~7 Citings

10. Cannabinoid receptors as therapeutic targets in the management of liver diseases

By Mallat, Ariane; Lotersztajn, Sophie
From Drug News & Perspectives (2008), 21(7), 363-368. Language: English, Database: CAPLUS, DOI:10.1358/dnp.2008.21.7.1255306

Despite recent advances in the understanding of mechanisms underlying the pathogenesis of liver diseases, therapeutic agents are still needed in several instances such as nonalcoholic fatty liver disease, alc. liver disease or fibrogenesis assocd. with chronic liver injury. Over the past decades, cannabinoid receptors have emerged as crit. mediators of acute and chronic liver injury, and pharmacol. modulation of these receptors has demonstrated efficacy in preclin. models of nonalcoholic and alc. fatty liver, fibrosis, liver ischemia reperfusion and of complications of cirrhosis, including cirrhotic portal hypertension, cirrhotic cardiomyopathy and hepatic encephalopathy. Moreover, CB1 antagonists have entered clin. trials for the management of nonalcoholic steatohepatitis. This review will depict the pleiotropic functions of cannabinoid receptors in liver disease and highlight potential therapeutic applications, some of which may be available in the near future.

~5 Citings

11. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects

By Izzo, A. A.; Camilleri, M.
From Gut (2008), 57(8), 1140-1155. Language: English, Database: CAPLUS, DOI:10.1136/gut.2008.148791

A review. A multitude of physiol. effects and putative pathophysiol. roles have been proposed for the endogenous cannabinoid system in the gastrointestinal tract, liver and pancreas. These range from effects on epithelial growth and regeneration, immune function, motor function, appetite control, fibrogenesis and secretion. Cannabinoids have the potential for therapeutic application in gut and liver diseases. Two exciting therapeutic applications in the area of reversing hepatic fibrosis as well as antineoplastic effects may have a significant impact in these diseases. This review critically appraises the exptl. and clin. evidence supporting the clin. application of cannabinoid receptor-based drugs in gastrointestinal, liver and pancreatic diseases. Application of modern pharmacol. principles will most probably expand the selective modulation of the cannabinoid system peripherally in humans. We anticipate that, in addn. to the approval in several countries of the CB1 antagonist, rimonabant, for the treatment of obesity and assocd. metabolic dysfunctions, other cannabinoid modulators are likely to have an impact on human disease in the future, including hepatic fibrosis and neoplasia.

~51 Citings

12. The endocannabinoid system and liver diseases

By Caraceni, P.; Domenicali, M.; Bernardi, M.
From Journal of Neuroendocrinology (2008), 20(Suppl. 1), 47-52. Language: English, Database: CAPLUS, DOI:10.1111/j.1365-2826.2008.01679.x

A review. Endogenous cannabinoids (EC) are ubiquitous lipid signaling mols. provided by a no. of central and peripheral effects, which are mainly mediated by the specific cannabinoid receptors CB1 and CB2. Although the expression of these receptors is very low or even absent in the healthy liver, a considerable series of exptl. studies and some clin. observations have recognized the EC system as an important player in the pathophysiol. of liver diseases. The EC system is highly up-regulated during chronic liver diseases and, to date, it has been implicated in the pathogenesis of non-alc. fatty liver disease, progression of fibrosis to cirrhosis and the development of the cardiovascular abnormalities of cirrhosis, such as the hyperdynamic circulatory syndrome and cirrhotic cardiomiopathy. Furthermore, the EC system influences the mechanisms responsible for cell damage and the inflammatory response during acute liver injury, such as that resulting from ischemia-reperfusion. Thus, mols. targeting the CB1 and CB2 receptors may represent potential therapeutic agents for the treatment of liver diseases. At present, the CB1 antagonists represent the most attractive pharmaceutical tool to resolve fat accumulation in patients with non-alc. fatty liver disease and to treat patients with cirrhosis, as they may slow the progression of fibrosis and attenuate the cardiovascular alterations assocd. with the advanced stage of the disease.

~2 Citings

13. Endocannabinoids and liver disease. III. Endocannabinoid effects on immune cells: implications for inflammatory liver diseases

By Pacher, Pal; Gao, Bin
From American Journal of Physiology (2008), 294(4, Pt. 1), G850-G854. Language: English, Database: CAPLUS, DOI:10.1152/ajpgi.00523.2007

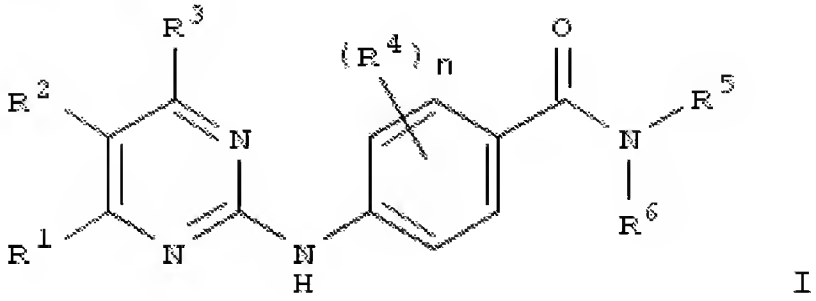
A review. Recent studies have implicated dysregulation of the endocannabinoid system in various liver diseases and their complications (e.g., hepatitis, fibrosis, cirrhosis, cirrhotic cardiomyopathy, and ischemia-reperfusion), and demonstrated that its modulation by either cannabinoid 2 (CB2) receptor agonists or CB1 antagonists may be of significant therapeutic benefits. This review is aimed to focus on the triggers and sources of endocannabinoids during liver inflammation and on the novel role of CB2 receptors in the interplay between the activated endothelium and various inflammatory cells (leukocytes, lymphocytes, etc.), which play pivotal role in the early development and progression of inflammatory and other liver diseases.

~16 Citings

14. Treatment for non-alcoholic-steatohepatitis and other related diseases

By Beraza, Naiara; Dreano, Michel; Trautwein, Christian
From PCT Int. Appl. (2008), WO 2008040548 A2 20080410, Language: English, Database: CAPLUS

The present invention provides methods of treating a subject with non- alc. fatty liver disease (NAFLD), insulin resistance, obesity or hyperlipidemia, comprising administering to the subject an effective amt. of a pyrimidin-2-ylaminobenzoyl compd. I (R1 = aryl, heteroaryl; R2 = H; R3 = H, lower alkyl; R4 = halo, OH, lower alkyl, lower alkoxy; n = 0-4; R5, R6 = H, alkyl, etc., or together with the nitrogen form an optionally substituted heterocycle) or a physiol. acceptable salt thereof. The administration of Compd. A (1-[4-[4-[4-(4-Chlorophenyl)pyrimidin-2-ylamino]benzoyl]piperazin-1-yl]ethanone) to mice with dietary induced NASH resulted in a clear improvement in obesity, insulin resistance, visceral fat accumulation, inflammation, lipid accumulation, lipid catabolism, oxidative stress and hepatocyte apoptosis and liver fibrosis.



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~0 Citings

15. The endocannabinoid system, a new pathway for treating hepatic fibrosis

By Teixeira-Clerc, F.; Julien, B.; Grenard, P.; Nhieu, J. Tran Van; Deveaux, V.; Hezode, C.; Mallat, A.; Lotersztajn, S.
From Pathologie Biologie (2008), 56(1), 36-38. Language: English, Database: CAPLUS,
DOI:10.1016/j.patbio.2007.01.001

A review. The cannabinoid system comprises specific G protein-coupled receptors (CB1 and CB2), exogenous (marijuana-derived cannabinoids) and endogenous (endocannabinoids) ligands, and a machinery dedicated to endocannabinoid synthesis and degrdn. Studies over two decades have extensively documented the crucial role of the cannabinoid system in the regulation of a variety of pathophysiol. conditions. However, its role in liver pathol. has only been recently unravelled, probably given the low expression of CB1 and CB2 in the normal liver. We have recently demonstrated that CB1 and CB2 receptors display opposite effects in the regulation of liver fibrogenesis during chronic liver injury. Indeed, both receptors are up-regulated in the liver of cirrhotic patients, and expressed in liver fibrogenic cells. Moreover, CB1 receptors are profibrogenic and accordingly, the CB1 antagonist rimonabant reduces fibrosis progression in three exptl. models. In keeping with these results, daily cannabis smoking is a risk factor for fibrosis progression in patients with chronic hepatitis C. In contrast, CB2 display antifibrogenic effects, by a mechanism involving redn. of liver fibrogenic cell accumulation. These results may offer new perspectives for the treatment of liver fibrosis, combining CB2 agonist and CB1 antagonist therapy.

~4 Citings

16. Blocking the cannabinoid receptors: drug candidates and therapeutic promises

By Muccioli, Giulio G.
From Chemistry & Biodiversity (2007), 4(8), 1805-1827. Language: English, Database: CAPLUS,
DOI:10.1002/cbdv.200790153

A review. The CB1 and CB2 cannabinoid receptors have been described as two prime sites of action for endocannabinoids. Both the localization and pharmacol. of these two G-protein-coupled receptors are well-described, and numerous selective ligands have been characterized. The physiol. effects of Cannabis sativa (cannabis) and a throughout study of the endocannabinoid system allowed for the identification of several pathophysiol. conditions - including obesity, dyslipidemia, addictions, inflammation, and allergies - in which blocking the cannabinoid receptors might be beneficial. Many CB1 receptor antagonists are now in clin. trials, and the results of several studies involving the CB1 antagonist lead compd. rimonabant (SR141716A) are now available. This review describes the pharmacol. tools that are currently available and the animal studies supporting the therapeutic use of cannabinoid receptor antagonists and inverse agonists. The data available from the clin. trials are also discussed.

~20 Citings

17. Reefer madness? Assessing the effects of cannabinoids with a less jaundiced eye

By Friedman, Scott L.
From Journal of Hepatology (2007), 46(1), 180-182. Language: English, Database: CAPLUS,
DOI:10.1016/j.jhep.2006.10.001

A review with commentary on the title research of F. Teixeira-Clerc, B. Julien, P. Grenard, J. Tran Van Nhieu, V. Deveaux, L. Li, et al. (2006). CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. Teixeira-Clerc F, Julien B, Grenard P, Tran Van Nhieu J, Deveaux V, Li L, Serriere-Lanneau V, Ledent C, Mallat A, Lotersztajn S. Hepatic fibrosis, the common response assocd. with chronic liver diseases, ultimately leads to cirrhosis, a major public health problem worldwide. We recently showed that activation of hepatic cannabinoid CB2 receptors limits progression of exptl. liver fibrosis. We also found that during the course of chronic hepatitis C, daily cannabis use is an independent predictor of fibrosis progression. Overall, these results suggest that endocannabinoids may drive both CB2-mediated antifibrogenic effects and CB2-independent profibrogenic effects. Here we investigated whether activation of cannabinoid CB1 receptors (encoded by Cnr1) promotes progression of fibrosis. CB1 receptors were highly induced in human cirrhotic samples and in liver fibrogenic cells. Treatment with the CB1 receptor antagonist SR141716A decreased the wound-healing response to acute liver injury and inhibited progression of fibrosis in three models of chronic liver injury. We saw similar changes in Cnr1-/- mice as compared to wild-type mice. Genetic or pharmacol. inactivation of CB1 receptors decreased fibrogenesis by lowering hepatic transforming growth factor (TGF)-β1 and reducing accumulation of fibrogenic cells in the liver after apoptosis and growth inhibition of hepatic myofibroblasts. In conclusion, our study shows that CB1 receptor antagonists hold promise for the treatment of liver fibrosis.

~1 Citing

18. CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis

By Teixeira-Clerc, Fatima; Julien, Boris; Grenard, Pascale; Van Nhieu, Jeanne Tran; Deveaux, Vanessa; Li, Liying; Serriere-Lanneau, Valerie; Ledent, Catherine; Mallat, Ariane; Lotersztajn, Sophie
From Nature Medicine (New York, NY, United States) (2006), 12(6), 671-676. Language: English, Database: CAPLUS, DOI:10.1038/nm1421

Hepatic fibrosis, the common response assocd. with chronic liver diseases, ultimately leads to cirrhosis, a major public health problem worldwide. We recently showed that activation of hepatic cannabinoid CB2 receptors limits progression of exptl. liver fibrosis. We also found that during the course of chronic hepatitis C, daily cannabis use is an independent predictor of fibrosis progression. Overall, these results suggest that endocannabinoids may drive both CB2-mediated antifibrogenic effects and CB2-independent profibrogenic effects. Here we investigated whether activation of cannabinoid CB1 receptors (encoded by Cnr1) promotes progression of fibrosis. CB1 receptors were highly induced in human cirrhotic samples and in liver fibrogenic cells. Treatment with the CB1 receptor antagonist SR141716A decreased the wound-healing response to acute liver injury and inhibited progression of fibrosis in three models of chronic liver injury. We saw similar changes in Cnr1-/- mice as compared to wild-type mice. Genetic or pharmacol. inactivation of CB1 receptors decreased fibrogenesis by lowering hepatic transforming growth factor (TGF)-β1 and reducing accumulation of fibrogenic cells in the liver after apoptosis and growth inhibition of hepatic myofibroblasts. In conclusion, our study shows that CB1 receptor antagonists hold promise for the treatment of liver fibrosis.

~166 Citings

19. Antagonists of the CB1 cannabinoid receptor for the treatment of fibrotic diseases of the liver

By Lotersztajn, Sophie; Mallat, Ariane; Grenard, Pascale; Julien, Boris; Nhieu, Jeanne Tran Van
From Eur. Pat. Appl. (2005), EP 1574211 A1 20050914, Language: English, Database: CAPLUS

The invention relates to the use of antagonists to the CB1 cannabinoid receptor for the prepn. of a compn. for the treatment of hepatic diseases and preferably to the use of Rimonabant (N-piperidino-5-(4-chlorophenyl)-1-(2, 4-dichloropenyl)-4-methylpyrazole-3-carboxamide). The mRNA for the CB1 receptor is more abundant in cirrhotic liver than in healthy liver. Mice lacking the CB1 receptor are more resistant to fibrotic change in the liver.

~2 Citings

20. Cannabinoid Receptor Type I Modulates Alcohol-Induced Liver Fibrosis

By Patsenker Eleonora; Stoll Matthias; Millonig Gunda; Agaimy Abbas; Wissniowski Till; Schneider Vreni; Mueller Sebastian; Brenneisen Rudolf; Seitz Helmut K; Ocker Matthias; et al
From Molecular medicine (Cambridge, Mass.) (2011), , Language: English, Database: MEDLINE

The cannabinoid system (CS) is implicated in the regulation of hepatic fibrosis, steatosis and inflammation, with cannabinoid receptors (CB) 1 and 2 being involved in regulation of pro- and anti-fibrogenic effects. Daily cannabis smoking is an independent risk factor for the progression of fibrosis in chronic hepatitis C and a mediator of experimental alcoholic steatosis. However, the role and function of CS in alcoholic liver fibrosis (ALF) is unknown so far. Thus, human liver samples from patients with alcoholic liver disease (ALD) were collected for analysis of CB1 expression. In vitro, hepatic stellate cells (HSC) underwent treatment with acetaldehyde, H(2)O(2), endo- and exocannabinoids (2-arachidonoylglycerol (2-AG) and Δ9-tetrahydrocannabinol (THC)), and CB1 antagonist SR141716 (Rimonabant). In vivo, CB1 knock-out (KO) mice received thioacetamide (TAA)/ethanol (EtOH) to induce fibrosis. As a result, in human ALD CB1 expression was restricted to areas with advanced fibrosis only. In vitro, acetaldehyde, H(2)O(2), as well as 2-AG and THC, alone or in combination with acetaldehyde, induced CB1 mRNA expression, whereas CB1 blockage with SR141716 dose-dependently inhibited HSC proliferation, downregulated mRNA expression of fibrosis-mediated genes PCα1(I), TIMP-1 and MMP-13. This was paralleled by marked cytotoxicity of SR141716 at high doses (5-10μM). In vivo, CB1 knockout mice showed marked resistance to alcoholic liver fibrosis. In conclusion, CB1 expression is upregulated in human ALF which is at least in part triggered by AA and oxidative stress. Inhibition of CB1 by SR141716, or via genetic knock-out protects against alcoholic-induced fibrosis in vitro and in vivo.

~0 Citings

21. Endocannabinoids and their role in fatty liver disease

By Mallat A; Lotersztajn S
From Digestive diseases (Basel, Switzerland) (2010), 28(1), 261-6, Language: English, Database: MEDLINE

The endocannabinoid system comprises receptors, CB1 and CB2, their endogenous lipidic ligands and machinery dedicated to endocannabinoid synthesis and degradation. An overactive endocannabinoid system appears to contribute to the pathogenesis of several diseases, including liver diseases. With the increasing incidence of non-alcoholic fatty liver disease (NAFLD) in parallel with the obesity epidemic, the development of effective therapies is gaining considerable interest. Several recent experimental lines of evidence identify CB receptors as potential novel therapeutic targets in the management of NAFLD. Endogenous activation of peripheral CB1 receptors is a key mediator of insulin resistance and enhances liver lipogenesis in experimental models of NAFLD. Moreover, we have shown that adipose tissue CB2 receptors are markedly upregulated and promote fat inflammation, thereby contributing to insulin resistance and liver steatosis. Data from our group also indicate that tonic activation of CB1 receptors is responsible for progression of liver fibrosis, whereas CB2 receptors display anti-fibrogenic properties. The clinical relevance of these findings is supported by studies in patients with chronic hepatitis C indicating that daily cannabis use is an independent predictor of both fibrosis and steatosis severity. Moreover, preliminary data derived from clinical trials strongly suggest that selective CB1 antagonism improves insulin resistance and reduces liver fat. Tempering these promises, the first generation of CB1 antagonists raised concern due to an alarming rate of mood disorders and the development program of these molecules was suspended. Current research efforts are therefore focused on developing formulations of CB1 antagonists that do not enter the central nervous system, and preliminary experimental data obtained with such molecules are encouraging.

~0 Citings

22. CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis

By Wasmuth Hermann E; Trautwein Christian
From Hepatology (Baltimore, Md.) (2007), 45(2), 543-4, Language: English, Database: MEDLINE

~0 Citings

23. Cannabinoid receptors as new targets of antifibrosing strategies during chronic liver diseases

By Mallat Ariane; Teixeira-Clerc Fatima; Deveaux Vanessa; Lotersztajn Sophie
From Expert opinion on therapeutic targets (2007), 11(3), 403-9, Language: English, Database: MEDLINE

Chronic liver injury exposes the patient to liver fibrosis and its end stage, cirrhosis, is a major public health problem worldwide. In western countries, prevailing causes of cirrhosis include chronic alcohol consumption, hepatitis C virus infection and non-alcoholic steatohepatitis. Current treatment of hepatic fibrosis is limited to withdrawal of the noxious agent. Nevertheless, suppression of the cause of hepatic injury is not always feasible and numerous efforts are directed at the development of liver-specific antifibrotic therapies. Along these lines, the authors recently demonstrated that the endocannabinoid system shows promise as a novel target for antifibrotic therapy during chronic liver injury. Indeed, cannabinoid receptors CB1 and CB2 promote dual pro- and antifibrogenic effects, respectively. Therefore, endocannabinoid-based therapies, combining CB2 agonists and CB1 antagonists may open novel therapeutic perspectives for the treatment of chronic liver diseases.

~5 Citings

24. CB1 cannabinoid receptor antagonists: a novel approach for the treatment of liver fibrosis

By Teixeira-Clerc Fatima; Julien Boris; Grenard Pascale; Tran Van Nhieu Jeanne; Deveaux Vanessa; Li Liying; Serriere-Lanneau Valerie; Ledent Catherine; Mallat Ariane; Lotersztajn Sophie
From Medecine sciences : M/S (2006), 22(8-9), 683-5, Language: French, Database: MEDLINE

~0 Citings